TWO BARRIER CROSSING PROBLEMS IN BIOMEMBRANES : POLYMER TRANSLOCATION AND PORE GROWTH(Session III : Complex Fluids, The 1st Tohwa University International Meeting on Statistical Physics Theories, Experiments and Computer Simulations)

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The biological systems described as soft matter in mesoscopic level manifest, in contrast to hard (condensed) matter, a number of characteristics, their structural complexity, flexibility and susceptibility to thermal fluctuation. Due to these, there arise at physiological temperatures a variety of conformational and dynamic phase transitions characteristic of living states. Here we investigate two examples of dynamical phase transitions involving biological membranes, polymer translocation and pore growth in membranes(Fig. 1).

The dynamics or the dynamic phase transition in a biological soft matter in mesoscopic scales is often described by a stochastic process crossing over a free energy function $F(x)$ (Fig. 2), where x is a relevant dynamic variable or order parameter. In Markovian model, the coarse-grained dynamics for $x(t)$ is given by a Langevin equation, or equivalently by the Fokker-Planck equation for its distribution function $P(x,t)$,

$$\frac{\partial}{\partial t}P(x,t) = L_{FP}(x)P(x,t) \;=\; D\frac{\partial}{\partial x}\left[\frac{\partial}{\partial x} + \beta\frac{\partial F(x)}{\partial x}\right]P(x,t), \tag{1}$$

where $D = k_B T/\zeta$ is the effective diffusion constant. An important information on the dynamical processes is the mean first passage time τ, the time crossing the free energy barrier from a local metastable state(x_0) to a global equilibrium, given by

$$L_{FP}^{\dagger}(x_0)\tau(x_0) = -1, \tag{2}$$

where $L_{FP}^{\dagger}$ is the adjoint of the Fokker-Planck opeartor L_{FP}.

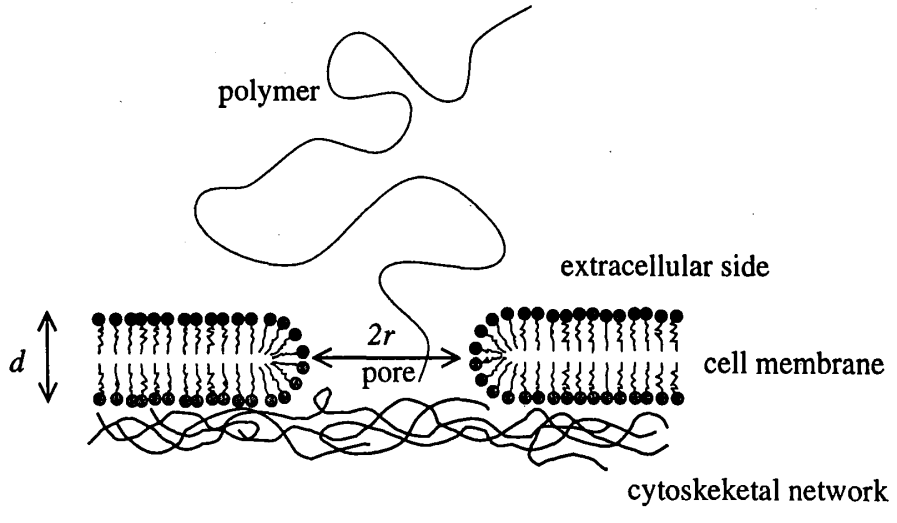

Figure 1: Polymer translocation and pore growth in a membrane

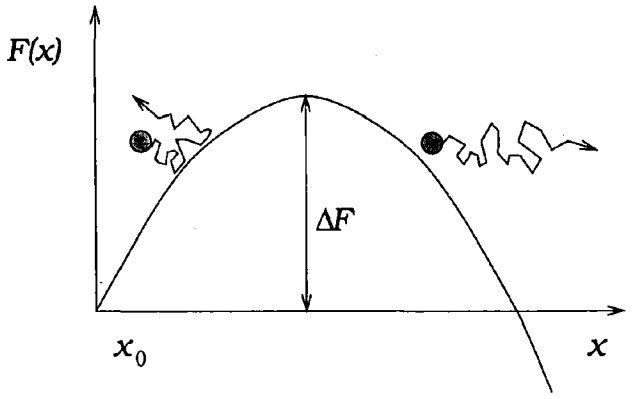

Figure 2: Free energy barrier with dynamic variables $x = n$ for polymer translocation and $x = r$ for pore growth.

As an application of this Markovian theory, we describe the translocation of polymers through a pore in a planar membrane, which, along with their associated conformations, represents one of the central issues in cell biology and biotechnology[1]. We assume a model of a long ideal-chain with $N(\gg 1)$ Kuhn segments(each with length l) threaded through a fixed pore small enough to allow passage of only single segment. In this problem, the relevant dynamical variable x is n, the number of segments that have translocated to the intracellular side.

The free energy function $F(n)$, due to the entropic barrier polymer experiences, is given by

$$F(n) = \frac{k_B T}{2} \log n(N-n) - n\Delta\mu, \tag{3}$$

where $\Delta\mu = \mu_o - \mu_i$ is the difference between chemical potentials per segment in extracellular and intracellular sides. The chain friction constant is $\zeta = N\gamma$, with γ being segmental friction coefficient. The translocation time of the chain, defined as the mean first passage time from $n = 1$ to $n = N$ without returning to the extracellular side, is calculated to be

$$\tau = \frac{\pi^2}{16}\frac{N^3 l^2 \gamma}{k_B T} \qquad (\text{for } \Delta\mu = 0) \tag{4}$$

$$\tau \simeq \frac{N^2 l^2 \gamma}{\Delta\mu} \qquad (\text{for } \Delta\mu > k_B T/N). \tag{5}$$

Remarkably the translocation is a dynamic transition or crossover from $\tau \sim N^3$ to $\tau \sim N^2$ scaling behavior which can be driven by a very minute chemical potential difference for a long chain.

We also consider an asymmetry effect caused by Brownian Ratchets(BRs) acting(such as chaperonin binding) on intracellular part of the chain, keeping it from tracing back. With $M(\gg 1)$. BRs bound, the translocation time is given as

$$\tau = \frac{L^2}{2DM} g(M, N), \tag{6}$$

where

$$g(M, N) \cong 1 + (2MN^{-1/4})^{-4/5}. \tag{7}$$

Here $L = Nl$ is chain contour length and $D = k_BT/N\gamma$ is (Rouse) diffusion constant of the chain. For $M \gg N^{1/4}$, the ratchets suppress chain flexibility, yielding $g \simeq 1$, *i.e.* $\tau \simeq L^2/(2DM)$, the translocation time of a rigid rod of length L[1]. Otherwise, the chain flexibility retards translocation by the factor $g > 1$. Furthermore, if the number of ratchets M is proportional to N, the translocation undergoes a dynamic transition to the scaling behavior $\tau \sim N^2$.

The other problem is dynamics of pore growth in a membrane in response to thermal fluctuation, transmembrane potential, the membrane and its environment. The pore growth induced by strong electric fields applied on cells, called electroporation, enhances dramatically transport of polymers, such as proteins and DNAs, as well as ions across the membranes. The electroporation as well as the fusion of these electrically destabilized membranes bring about novel biotechnological applications such as gene transfer and cell fusion[2].

We consider a single pore already formed in a membrane, both of which are immersed in solvent. We regard the membrane as a two-dimensional dielectric and viscoelastic fluid continuum responding dynamically to the pore growth, which we model as a nonMarkovian stochastic process described by the generalized Langevin equation for pore radius $r(t)$,

$$-\zeta_s\dot{r}(t) - \int_{-\infty}^{t} dt'\xi(t-t')\dot{r}(t') - \frac{\partial F(r)}{\partial r} + f(t) = 0. \tag{8}$$

The $F(r)$, the free energy of formation of a pore with radius r, is given by

$$F(r) = -\pi\sigma r^2 + 2\pi\lambda r, \tag{9}$$

where σ and λ are surface tension and line edge energy. The $f(t)$ is a Gaussian colored noise related to the friction via fluctuation-dissipation theorem $\langle f(t)f(t')\rangle = k_BT\,[2\zeta_s\delta(t-t') + \xi(t-t')]$. The $\xi(t)$ is the memory function descriptive of viscoelastic relaxation of the fluid membrane. Using linearized equations of viscoelastic hydrodynamics, we obtain

$$\xi(t) = \frac{4\pi\eta d}{\tau_\eta}\exp(-t/\tau_\eta), \tag{10}$$

where η, τ_η, d are respectively the viscosity, viscoelastic relaxation time (which is macroscopically large, $\tau_\eta \simeq 0.1$ sec.), and thickness of the fluid membrane.

The nonMarkovian extension of Kramers' Markovian theory by Grote and Hynes[3] can be adapted to this barrier crossing problem. Defining the membrane lifetime τ as the mean first passage time of the pore state from $r = 0$ to $r = \infty$, we find that the memory effect renormalizes the Markovian lifetime τ_K (for membrane with friction ζ_s only) given by Eq. (2) to

$$\frac{\tau}{\tau_K} \simeq \begin{cases} 1 & , k \gg K \\ (\zeta_M/\zeta_s)^{1/2} & , k = K \\ \zeta_M/\zeta_s & , k < K. \end{cases} \tag{11}$$

Here $\zeta_M = 4\pi\eta d$ is the long-time membrane friction much larger than the short-time friction ζ_s. It is remarkable that the memory effect always stabilizes the membrane against pore growth, enhancing dramatically lifetime when $K \equiv \zeta_M\tau_\eta^{-1}$, the memory-induced elasticity, exceeds $k \equiv 2\pi\sigma$.

The environmental effects from applied transmembrane potential[4] and cytoskeletal network modify the value of σ in as much variety as the solvent conditions. The Fig. 3 shows

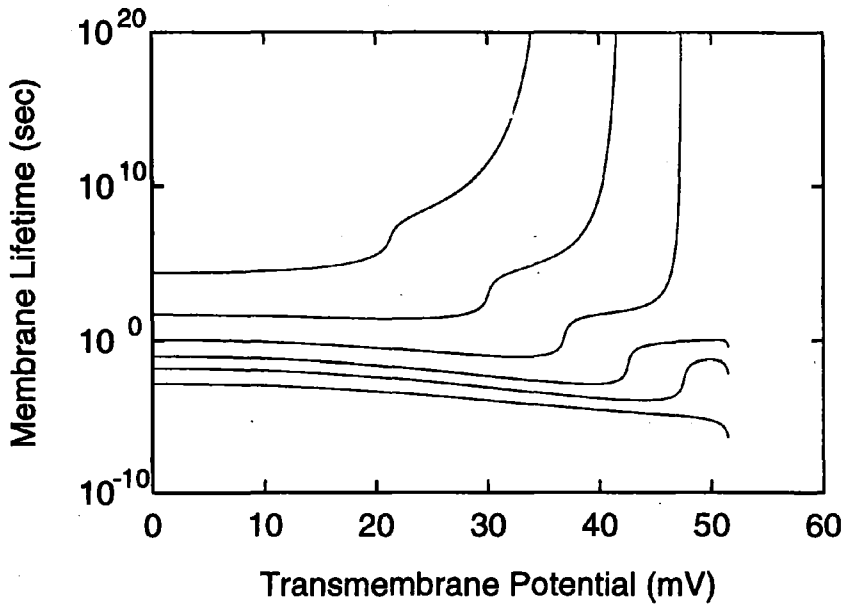

Figure 3: Membrane lifetime(τ) versus transmembrane potential difference(U) for various values of $\sigma(U=0)$ (3×10^{-6} N/m, 4×10^{-6} N/m, 5×10^{-6} N/m, 6×10^{-6} N/m, 7×10^{-6} N/m, 9×10^{-6} N/m from upper to lower curves), and $\lambda(U=0)=3\times10^{-13}$ N, $\zeta_s=5\times10^{-13}$ N sec/m, $\eta d\tau_\eta^{-1}=10^{-6}$ N/m, $\tau_\eta=0.1$ sec, $T=300$K.

the effects of various σ on our calculated membrane lifetime as a function of transmembrane potential U. Interesting bifurcative behavior follows after stepwise enhancement of lifetime due to the memory effect, for various values of k approaching the critical value corresponding to a natural membrane potential $U\simeq50$ mV.

In the combined picture(Fig. 1) of polymer translocation and pore growth in a membrane, there are many degrees of freedom on the scene competing with each other. Especially near the critcal conditions, *e.g.* the bifurcation points, where minute fluctuations or changes induce sharp dynamic transitions, such competitions are matter of life or death. A protein which strives to get into the cell should manipulate an environmental asymmetry or the chain rigidity. A membrane in need of protecting the cell from the protein should prohibit pore growth by modulating the solvent and the cytoskeletons. In addition, the memory effect(persistence) and stochastic resonance due to fluctuating free energy will compete to increase and decrease τ. These are uniquely due to the flexibility and complexity of soft matter in mesoscopic level, and can be relevant concepts for the important paradigm of biological self-organization.

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